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Das Reagenz · The Reagent

Manganese(III) acetate – A Versatile Reagent for Radical Generation and C–C Bond Formation

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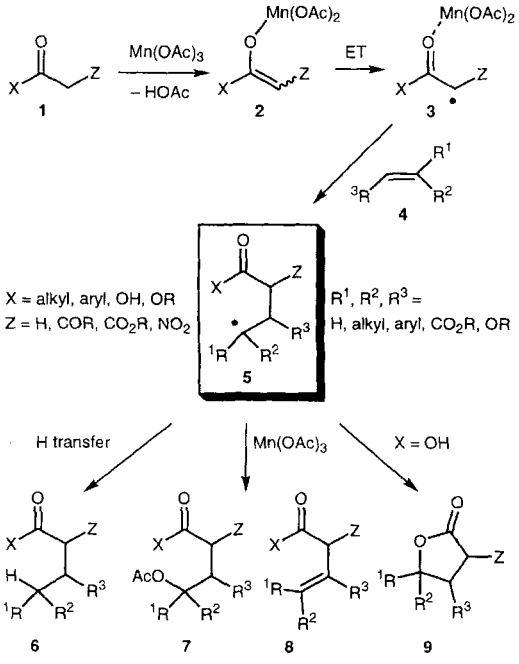
During the past decade radical reactions have become increasingly attractive for carbon–carbon bond formation and the synthesis of highly functionalized molecules [1]. Despite the mild reaction conditions and the broad applicability of alkyl halides as radical precursors in the presence of tributyltin hydride, the toxicity of tin compounds is disadvantageous. Therefore, oxidative methods offer an interesting alternative for the generation of radicals from easily accessible CH-acidic substrates using transition-metal salts [2]. Among the various one-electron oxidants, manganese(III) acetate dihydrate represents the most widely employed reagent. It can be prepared conveniently from potassium permanganate and manganous acetate in acetic acid or purchased from several suppliers.

$$KMnO_4 + 5\ Mn(OAc)_2 \cdot 4H_2O \xrightarrow[100\ °C]{HOAc} 6\ Mn(OAc)_3 \cdot 2H_2O + KOAc$$

1 Mechanistic Considerations

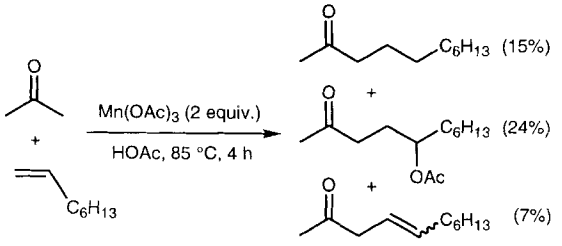
Since the pioneering work of Heiba and Bush in 1968 [3], the mechanism of manganese(III)-mediated radical reactions has been extensively studied. Fristad showed that the rate of radical generation with $Mn(OAc)_3 \cdot 2H_2O$, which is actually an oxo-centered triangle of Mn(III) with bridging acetates, correlates with the enolizability and CH acidity of the substrates **1** [4]. The broad variety of suitable radical precursors **1** include carboxylic acids, ketones, malonates, β-keto esters, 1,3-diketones, and β-nitro esters. In the initial step of the reaction, manganese(III) enolates **2** are formed, which undergo fast electron transfer (ET) to afford the radicals **3** (Scheme 1). Due to the electron-withdrawing substituents, such radicals exhibit electrophilic character and add readily to electron-rich alkyl- and arylsubstituted alkenes **4**. Whether the first steps proceed within the ligand sphere of the metal or if free radicals **3** are involved, is still a matter of debate, and future investigations should open up mechanistic details.



Scheme 1

The product distribution of manganese(III)-induced C–C bond formations strongly depends on the substitution pattern of the adduct radical **5** and on the reaction conditions. Thus, low concentrations of $Mn(OAc)_3 \cdot 2H_2O$ favor hydrogen-atom abstraction from the solvent or starting material to afford the saturated products **6**. In competing reactions, an excess of oxidant results in the formation of acetates **7** and alkenes **8**, which becomes the predominant process especially for tertiary adduct radicals **5**. Finally, lactones **9** are obtained as the major products by manganese(III)-mediated additions of carboxylic acids (X = OH) to double bonds (Scheme 1).

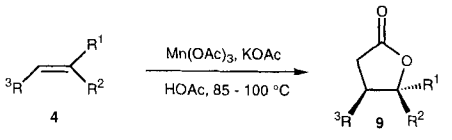
The problem of complex product mixtures became evident in one of Heiba's early examples of manganese(III)-mediated radical reactions (Scheme 2) [5]. Therefore, manganese(III) acetate was for a long time neglected as a versatile reagent for C–C bond formation. Nowadays various elegant methods are reported in literature to achieve high chemoselectivities by proper reaction conditions, and the potential of Mn $(OAc)_3 \cdot 2H_2O$ in organic synthesis is demonstrated in the following sections.



Scheme 2

2 Intermolecular Additions to C=C Double Bonds

The manganese(III)-induced addition of acetic acid to alkenes **4** provides a convenient one-pot entry to γ-lactones **9** (Scheme 3) [4–6]. The best yields are obtained in the presence of potassium acetate, which acts as a base and facilitates the

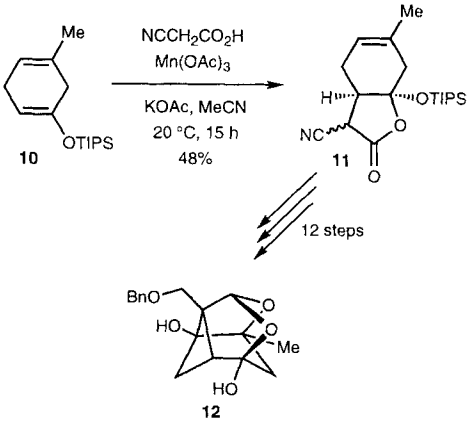


R^1	R^2	R^3	yield (%)
n-C_6H_{13}	H	H	74
n-C_6H_{13}	H	H	85
n-C_3H_7	H	*n*-C_3H_7	69
H	$-(CH_2)_5-$		75
Ph	H	H	60
Ph	Me	H	74
Ph	H	Me	79
Ph	H	CO_2Me	82
H	CO_2Et	CO_2Et	73
CO_2Et	H	CO_2Et	83

Scheme 3

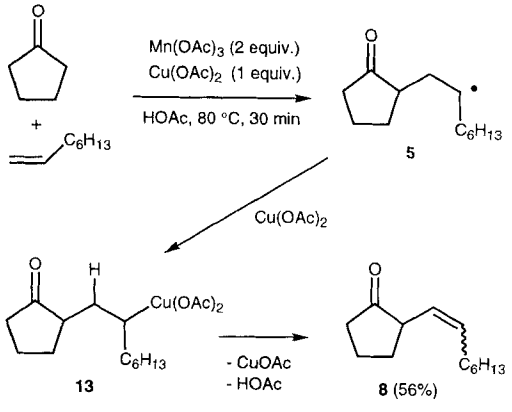
rate-determining deprotonation of the CH-acidic radical precursor. The high regioselectivities result from an orbital-controlled addition of the electrophilic radicals to the double bond as well as steric factors. Furthermore, all reactions exhibit a high degree of stereoselectivity, since the thermodynamically more stable *trans*-lactones **9** are formed as the major products. Various substituents R are tolerated under the reaction conditions and the annulations are not only limited to acetic acid, but can also be extended to chloroacetic, propanoic, malonic, and cyanoacetic acids [4].

Corey recently applied this methodology for the total synthesis of (±)-paeoniflorigenin (**12**), an active ingredient of the essential oils from *Paenonia lactiflora*, which is widely used in traditional Chinese medicine [7]. In the key step, the manganese(III)-mediated addition of cyanoacetic acid to the 1,4-cyclohexadiene **10** affords the bicyclic lactone **11** in moderate yield, but with high site-, regio-, and stereoselectivity (Scheme 4). The yields of such annulations can be substantially increased, if the reactions are performed under ultrasound irradiation [8].



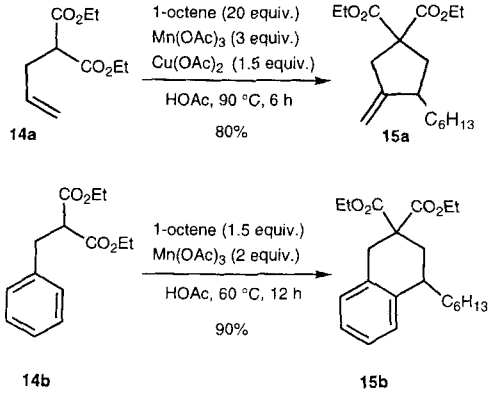
Scheme 4

The intermolecular addition of ketones to alkenes proceeds less efficiently than the lactonizations, since the various reaction pathways of adduct radicals **5** give only complex product mixtures (Scheme 1 and 2). Vinogradov developed a selective entry to the unsaturated products **8** by manganese(III)-induced reactions in the presence of cupric(II) acetate [9]. The mechanism involves copper(III) intermediates **13**, which undergo oxidative β-hydride elimination to afford the desired products in moderate yield (Scheme 5). Another



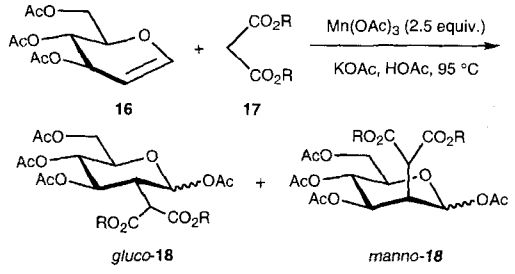
Scheme 5

attractive strategy consists of intramolecular trapping of the adduct radicals **5** by addition to double bonds [10] or arenes [11] and subsequent oxidation. This addition–cyclization sequence provides high yields of C–C-bonded products **15** from easily accessible malonic esters **14** (Scheme 6).



Scheme 6

Very recently, manganese(III)-mediated radical reactions were applied for the first time in carbohydrate chemistry [12]. Thus, addition of malonates **17** to the electron-rich double bond of tri-*O*-acetyl-D-glucal (**16**) proceeds in high regioselectivity, and provides an easy route to the *C*-analogues **18** in good yields (Scheme 7). The oxygen-substituted adduct radicals are readily oxidized by $Mn(OAc)_3 \cdot 2H_2O$ to cations, which are trapped by the solvent acetic acid. Since the stereoselectivity can be increased by variation of the substituents, this methodology should open up interesting prospects for the synthesis of *C*-branched carbohydrates.

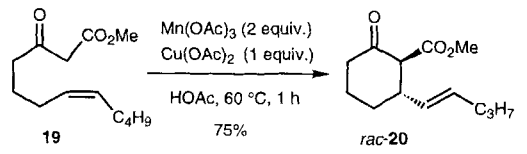


R	yield (%)	*gluco* : *manno*
Me	66	78 : 22
i-Pr	69	84 : 16

Scheme 7

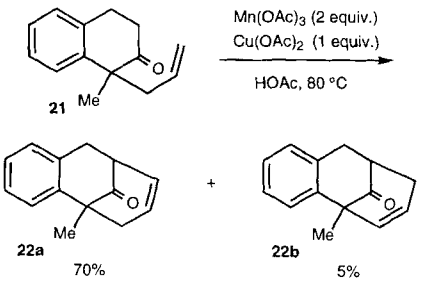
3 Intramolecular Additions to C=C Double Bonds

Manganese(III)-mediated cyclizations are mainly based on the pioneering and extensive studies of Snider, which were recently comprehensively reviewed [2]. One of the first examples demonstrates the potential of this methodology for the construction of five- and six-membered rings (Scheme 8) [13].



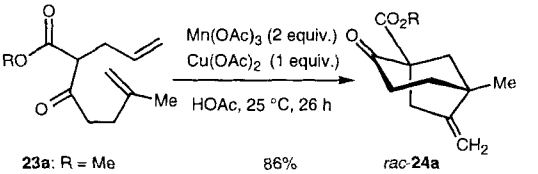
Scheme 8

Thus, reaction of β-keto ester **19** with $Mn(OAc)_3 \cdot 2H_2O$ affords the cyclohexanone **20** highly regio- and stereoselectively in 75% yield. The radical is generated at the more acidic position and 6-*exo* cyclization is favored over the 7-*endo* mode. Again, the presence of cupric(II) acetate is essential to obtain the unsaturated product. More recently, Snider extended intramolecular manganese(III)-induced additions to less CH-acidic ketones [14]. A representative example is the facile oxidative cyclization of the tetralone derivative **21** to the tricyclic products **22** in high yield (Scheme 9).



Scheme 9

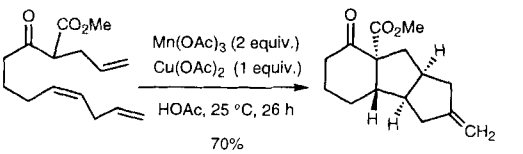
Manganese(III) acetate represents a powerful and versatile reagent for radical tandem cyclizations. The broad variety of suitable CH-acidic precursors range from β-keto acids, 1,3-diketones to malonic esters, but β-keto esters are most widely employed [2]. An instructive example exhibits the highly regio- and diastereoselective one-pot synthesis of the cyclohexanone derivative *rac*-**24a** from the methyl ester **23a** (Scheme 10)



23a: R = Me 86% *rac*-**24a**
23b: R = (–)-8-phenylmenthyl 90% (86% de) **24b**

Scheme 10

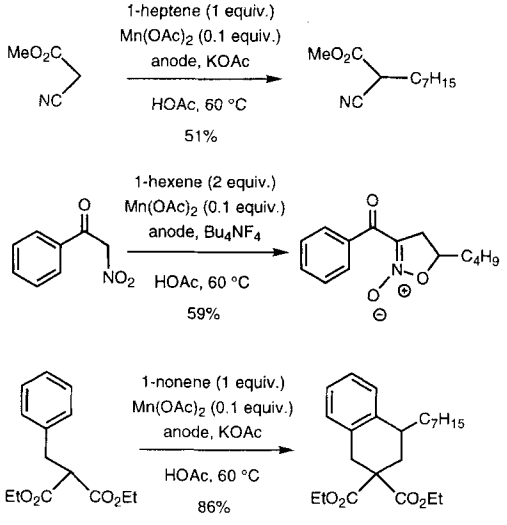
[15]. Furthermore, cyclization of the corresponding 8-phenylmenthyl ester **23b** proceeds with good asymmetric induction and affords the optically active product **24b** in high yield [16]. This methodology of auxiliary-directed, manganese(III)-mediated radical reactions was recently applied for the total synthesis of (+)-*O*-methylpodocarpic acid [17]. Finally, tandem cyclizations are not only limited to two consecutive additions, but can be efficiently used for the diastereoselective construction of polycyclic ring systems (Scheme 11) [15].



Scheme 11

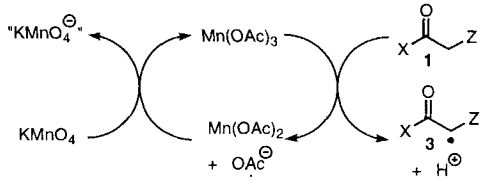
4 *In Situ* Generation of Manganese(III) Acetate

One major drawback of manganese(III)-induced C–C bond formations is the excess of oxidant required for complete conversion of the alkene, which becomes especially a problem for large-scale reactions. Therefore, methods for the *in-situ* generation of manganese(III) were developed during the last years. One attractive concept consists in the electrochemical oxidation of manganese(II) acetate to $Mn(OAc)_3 \cdot 2H_2O$ in an undivided cell. Some representative examples of additions to terminal alkenes are summarized in Scheme 12 [18]. The adduct radicals can either be trapped intramolecularly or by hydrogen-atom transfer from the solvent or the radical precursor, and only 10 mol% of $Mn(OAc)_2 \cdot 4\ H_2O$ are sufficient. Furthermore, the reactions can be performed on large scale, which was utilized for the industrial synthesis of sorbic acid from butadiene and acetic acid [19].

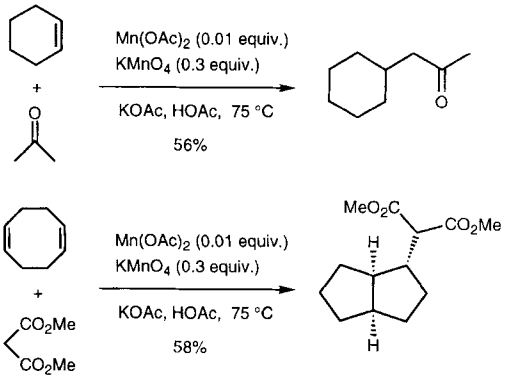


Scheme 12

Very recently an efficient protocol for the *in-situ* generation of $Mn(OAc)_3 \cdot 2H_2O$ from potassium permanganate and manganese(II) acetate in the presence of a CH-acidic precursor **1** was developed (Scheme 13) [20]. Only catalytic amounts of manganese(III) are involved in the reaction cycle, which allows the generation of the radicals **3** under "non-oxidative conditions". Thus, the hydrogen-atom transfer products **6** can be synthesized selectively without competing oxidations to acetates **7** or alkenes **8** (Scheme 1). The method is characterized by easily accessible starting materials and two representative examples are shown in Scheme 14.



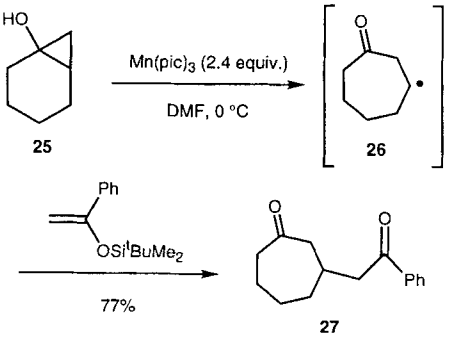
Scheme 13



Scheme 14

5 Future Prospects

One major problem of manganese(III)-mediated C–C bond formations are the rather drastic reaction conditions. Due to the poor solubility of $Mn(OAc)_3 \cdot 2H_2O$ in organic solvents, acetic acid is most widely used, which limits the number of functional groups that may be tolerated. To overcome this difficulty, Narasaka introduced manganese(III) tris(2-pyridinecarboxylate) ($Mn(pic)_3$) as a versatile substitute for manganese(III) acetate [21]. Cyclopropanols **25** represent suitable precursors and are opened smoothly to the corresponding β-carbonyl radicals **26** even at 0 °C in DMF (Scheme 15). The mild reaction conditions allow additions to acid-labile silyl enol ethers to afford the diketone **27** in good yield.



Scheme 15

Another challenging task are enantioselective manganese (III)-mediated C–C bond formations, which are hitherto unknown. Since the radical generation proceeds in the ligand sphere of the metal (Scheme 1), optically active manganese complexes might offer promising opportunities.

In view of the current interest in transition-metal-mediated radical reactions, new developments for synthetic applications are expected to appear in the near future.

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